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Translational control mechanism of HIV-1 *tat1* mRNA

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Background

The Human Immunodeficiency Virus type 1 Tat protein is a major viral transactivator which stimulates the synthesis of full length transcripts by interacting with the 5'end of all nascent viral RNAs. Translation of *tat* mRNAscan be cap dependent. Nevertheless, in phaseG2/M ribosomes translate *tat* mRNAs by an alternative initiation processdepending on anlnternal Ribosome Entry Site (IRES). This initiation is auto-stimulated by Tat [1]. Recently, SRp40 and SRp55 proteins were found to promote Gag IRES-dependent translation initiation [2]. Therefore, SR and hnRNP proteins likely play a key role in regulation of both splicing and translation of HIV-1 RNA. As we previously observed a binding of hnRNP H (3), DAZAP1 and various SR proteins in the vicinity of the *tat* initiation codon(4), we asked whether these proteins can regulate *tat* mRNA translation.

Materials and methods

To address this issue, we built mono and bicistronic constructs expressing a Tat-Renilla luciferase fusion protein or individual Tat and Renilla proteins, respectively. We used these constructs to studythe effect of an overexpression of SR and hnRNPproteins in Hela cells on the cap dependent and cap-independent*tat1* mRNA translation initiation. Efficiency of Tat production by the bi-cistronic construct was tested by measuring the Tat activity on a Firefly luciferase gene under the control of the HIV-1 LTR.

Results

Our data strongly suggest that hnRNP H, and some of the SR proteins (ASF-SF2 and 9G8)activate the *tat1* mRNA IRES, whileDAZAP1 inhibit its activity, and these regulationsdepends uponthe presence of the *tat1* mRNA5'UTR.

Conclusions

Altogether our data reveal a complex regulation of the internal initiation of *tat1* mRNA, that may reflect the situation in human cells infected by virus HIV-1.

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